REMARKS

After amendment, claims 4-10, 12, 13, 15, and 24 are pending. Claims 1, 2, 14 and 21-23 are cancelled. Applicant reserves the right to prosecute any cancelled claims, including claims 1, 2, and 14, and any cancelled subject matter in a continuation application filed during the pendency of the present application.

Claim 4 is amended by rewriting the same in independent form and incorporating all of the features of independent claim 1. Claims 5-10, 12 and 15 are amended to clarify the invention and to change the dependency of the same. Claim 24 is added to recite another embodiment of the invention. Specifically, claim 24 recites that the antisense oligonucleotide of claim 4 demonstrates at least 30% inhibition. That level of inhibition is not new matter as it is explicitly supported in the original specification at page 89, lines 21-25 and by fifteen of twenty-two specific examples provided in Table 1.

No new matter is added by these amendments. Applicants confirm the correctness of the inventive entity in view of these claim amendments and cancellations.

Information Disclosure Statement

> The Examiner has asserted that no translation has been provided for Toyama and has therefore not been considered.

Pursuant to 37 CFR § 1.97(3)(i), Applicant provided a concise explanation of the relevance of Toyama in the Supplemental Information Disclosure Statement filed May 6, 2003. Further, since a translation was not available to the inventors, Applicant, or below-noted attorney of

record, a translation of this document was not supplied pursuant to 37 CFR § 1.97(3)(ii). Applicant did however provide a copy of an Abstract of Toyama as document CG.

Reconsideration of document CB in view of the provided remarks and abstract is requested.

Election by Original Presentation

The Examiner has asserted that newly amended claim 1 and its dependent claims and newly submitted claims 21-23 are directed to inventions that are independent or distinct from that originally claimed.

(i) The Examiner has asserted that claim 1, reciting antisense sequences that target nucleobases 14 to 1741 of SEQ ID NO:3 is distinct from the complete SEQ ID NO: 3 and is considered to be elected by original presentation. Subsequent amendments directed to new, specific, and distinct regions of SEQ ID NO: 3 will be considered to effectively claim new and distinct targets, and be drawn to a new invention because each sequence is distinct, and requires a different search. The search for one target region does not reveal art against another. A search for art against the whole originally claimed target of SEQ ID NO: 3 does not result in a complete and exhaustive list of all art directed against all of the newly defined region.

(ii) Claims 21-23 are asserted to include new limitations that are unrelated to the originally filed invention of Claims 1, 2, 4-10 and 12-15 and have therefore been withdrawn.

Applicant respectfully requests reconsideration and withdrawal of this restriction for the following reason.

Claims 1-2 are canceled, thereby mooting the outstanding requirement as to them. Claim 4 is rewritten

in independent form and contains subject matter that falls under the elected subject matter.

Claims 22-23 are canceled thereby mooting the outstanding rejection as applied to these claims. Claim 21 is canceled, but is represented as new claim 24. Applicant respectfully asserts that claim 24 is not drawn to assays, but is instead drawn to a narrower percent inhibition encompassed by the language of broader amended claim 4 on which claim 24 depends. Thus, claim 24 does not require an additional search. Specifically, claim 24 recites that the antisense oligonucleotide of claim 4 demonstrates at least 30% inhibition of ACAT-1 gene expression. That level of inhibition is not new matter as it is explicitly supported in the original specification at page 89, lines 21-25 and by 15 specific examples in Table 1. It is clearly encompassed by claim 1's broader recitation of "at least 12% inhibition".

In view thereof, Applicant respectfully requests that the Examiner enter new claim 24 with pending claims 4-10 and 12-15.

Reconsideration is requested.

35 USC §§ 102/103 Rejection

> Claims 1, 2, and 12 are rejected under 35 USC § 102(e) and 103 (a) over International Patent Publication No. WO 01/16358 A2 (Borg-Capra)
>
> The Examiner has asserted the sequence on page 11, line 2 possesses 100% reverse identity with residues 1697-1721 of the instant application and would thus specifically hybridize with Applicant's claimed target region.

Applicant respectfully requests reconsideration and withdrawal of this rejection for the following reason.

In an effort to place the application in condition for allowance, Applicant has cancelled claims 1 and 2, amended claim 4, and amended claim 12 to depend from amended claim 4. Since now-independent claim 4 was not rejected on this basis, its dependent claims should also not be rejected on this basis. Therefore, this rejection is rendered moot by the above amendments, and should be withdrawn.

Reconsideration of this rejection is requested.

35 USC § 103 Rejection

> Claims 1, 2, 4-10, and 12-15 are rejected under 35 USC § 103(a) as allegedly obvious in view of the combination of US Patent No. 5,968,749 (Chang I) or US Patent No. 5,484,727 (Chang II), in view of US Patent No. 5,801,154 (Baracchini) and Taylor *et al.* **1999** *Drug Disc. Today*, 4(12):562-567 (Taylor).
>
> The Examiner has asserted that it would have been obvious to make antisense oligonucleotides to inhibit ACAT since its sequence and the use of antisense compounds to inhibit ACAT were allegedly taught by Chang I and II; and incorporate modifications of Baracchini into the antisense compounds of Chang; because Taylor teaches that inhibition of expression of any protein may be accomplished using a known cDNA sequence, and states that allegedly only 3-6 oligos are necessary to screen to find one that inhibits its target 66-95%.

Applicant respectfully requests reconsideration and withdrawal of this rejection for the following reason.

Claims 1, 2, and 14 have been canceled thereby mooting the outstanding rejection as applied to these claims.

With respect, Applicants assert the combination of Chang I and/or II, Baracchini and Taylor do not make a

prima facie obviousness rejection of the pending, amended claims 4 and 15 and their dependent claims for the following reasons.

(A) Taylor must be withdrawn as a basis for rejection as its statements are incorrect and misleading.

The review article, Taylor, adds nothing to the combination of Baracchini and Chang that would make obvious the invention of the pending amended claims. In fact, Taylor makes a misleading and unsupported allegation about the ease and straightforward manner of determining target sites on a gene that permit one to identify suitable antisense oligonucleotides of a high degree of inhibition for any gene. At page 565, col. 1, lines 3-11, Taylor alleges that screening 3-6 oligomers per target is sufficient to find one that inhibits any gene with 66-95% efficiency.

Applicants assert that this blanket statement in Taylor conveys a misleading impression to the examiner that identification of target sites that can be bound by antisense oligonucleotides to significantly inhibit gene expression is simple and expected. In fact, such techniques do not produce such "expected" and simple results as stated by Taylor.

As demonstrated by the accompanying Rule 132 Declaration, such a statement is not universally true of any gene at all. Applicants' assignee, which is a company that specializes in antisense technology and uses the latest in bioinformatics programs, has provided evidence in the declaration for two genes that one may investigate 80 or more oligonucleotides without success in identifying a target site permitting any level of inhibition. This evidence demonstrates that one of skill

in the art cannot *a priori* expect ease of target identification simply because antisense methodologies are known in general and a gene sequence is published. One cannot base an assumption as to what level, if any, of inhibition may be obtained from antisense sequences obtained for a gene in question from data gathered on another unrelated gene. Taylor simply cannot stand for this proposition.

In view of the evidence supplied by the attached Declaration, Applicants request that Taylor be withdrawn as a basis for combination with the other references in making this rejection. As the obviousness rejection is based upon a combination of Chang, Baracchini **and** Taylor, the removal of Taylor as a reliable reference defeats this ground of rejection.

(B) The Examiner is using the wrong standard in making the obviousness rejection.

The combination of the three documents Chang[1], Baracchini and Taylor at best provides only an indication that it is obvious ***to try*** to make an antisense sequence capable of inhibiting ACAT - this is ***NOT*** the proper standard for obviousness.

Chang refers to the cloning of a nucleic acid molecule encoding a human acyl coenzyme A:cholesterol actltransferase (ACAT), and the provision of a cell transformed with that nucleic acid molecule. The documents further teach a method of testing for an agent capable of inhibiting an ACAT by exposing an "agent" to a non-human cell **transfected** with a specific coding

[1] Chang I and II share the same specification and are thus referred to singly in this argument.

sequence for the ACAT and then inspecting the cell for inhibition of the ACAT enzyme activity. Moveover, Chang does not disclose methods of using such antisense compounds to inhibit **endogenous** ACAT expression in cells or tissues, such as is required by Applicants' amended claims 4 and 15.

The portion of the Chang specification that refers to the antisense compounds (see col. 5, lines 5-30 of Chang II) is extremely generic and can be found in any reference or review article discussing antisense technology. Chang does no more than provide a ***suggestion for testing*** for inhibitory activity of a generic antisense compound for which no description is provided. Chang does not teach or suggest any minimal level of inhibition of ACAT expression that is desirable.

No specific antisense compositions are disclosed or suggested by these documents. None of this teaching leads one to the specific sequence of nucleotide 14-1371 of the ACAT of SEQ ID NO: 3 referred to by Applicants' amended claims.

Baracchini adds nothing to Chang that provides the suggestions missing from Chang to make obvious the subject matter of the presently amended claims. In fact, taken for it generic antisense teachings, Baracchini does no more or less than simply reiterate Chang's generic teachings about antisense sequence. In fact Baracchini refers to antisense compounds that modulute a completely unrelated protein to ACAT, namely multi-drug resistance-associated protein (MRP). Baracchini contains no disclosure that suggests or refers to the protein ACAT. Without any disclosure of ACAT, Baracchini cannot provide any suggestion that permits one to identify or suggest

specific ACAT sequences of SEQ ID NO: 3 as target sequences for binding by a specific antisense sequence or provide any desired minimal level of inhibitory activity of ACAT antisense compounds. Baracchini does not teach or suggest any sequence for antisense compounds that bind to ACAT, as required by claim 1. Nor does Baracchini suggest any methods for using the sequences of claim 1. Baracchini does not teach or suggest a therapeutic utility of antisense compounds that bind ACAT.

Taylor's generic statements have been rebutted by the attached Declaration and should be given no weight in this rejection.

An obviousness rejection based on a combination of Baracchini's generic disclosures about antisense sequences in general (and specifically with regard to MRP) and Chang's disclosure of a method of testing an inhibitory agent to ACAT, which agent may be ***an unidentified, unspecific*** antisense sequence, coupled with Taylor's misleading conclusion of the expectedness and simplicity of active site identification on the target genes is defective. An obviousness rejection cannot be made by combining documents to make the bald suggestion that it is "obvious to try" to make antisense compounds to target ACAT.

Applicants are not claiming any and all antisense sequences that target any ACAT. Rather, Applicants' claims recite only sequences between 8 and 50 nucleobases in length that specifically hybridize within nucleotides 14-1741 of SEQ ID NO: 3 and which inhibit expression of the resulting enzyme ***by at least 12%*** in a cell ***endogenously*** expressing ACAT-1.

Taking each reference as a whole, the combination of Baracchini and Chang (Taylor being excluded for the above reasons) does not provide any *suggestion* of Applicants' specifically-claimed antisense sequences of claim 4, nor the method of claim 15. This combination does not provide the suggestion that the subject matter of Applicants' claims is expected or even likely to be useful for inhibiting gene expression.

In view of the above amendments and these remarks, Applicants' respectfully request that the examiner withdraw the outstanding rejections and permit the above pending claims to pass to issue in due course.

Reconsideration of this rejection is requested.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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